Penicillin sensitivity of gonococci isolated in Australia, 1981–6

AUSTRALIAN GONOCOCCAL SURVEILLANCE PROGRAMME*

SUMMARY The sensitivity to penicillin of about 25 000 gonococcal isolates tested in Australia during the five years to 30 June 1986 was assessed in a collaborative multicentric study. Increasing resistance to the penicillin group of antibiotics was observed during the course of this study and was manifested both as increased levels of chromosomally mediated intrinsic resistance and by an increasing incidence of penicillinase producing strains of *Neisseria gonorrhoeae* (PPNG). Pronounced regional differences in the levels of intrinsic resistance, the incidence of infections with PPNG, and the endemic spread of PPNG strains were observed.

Penicillin G and its analogues, in combination with probenecid, have remained an effective regimen for treating gonorrhoea in many parts of Australia despite increasing resistance to this group of antibiotics in strains of Neisseria gonorrhoeae. Gonococcal resistance to the penicillins may arise by either chromosomal or extrachromosomal mechanisms.1 Mutations in the bacterial chromosome lead to a series of incremental alterations in gonococcal sensitivity to penicillin, thus increasing the "intrinsic resistance" of the organisms. Gonococci may also acquire plasmids that code for the production of β lactamase, and such strains are called penicillinase producing Neisseria gonorrhoeae (PPNG) strains. Whereas increased intrinsic resistance can be accommodated to a large extent by increasing the dose of antibiotic administered. PPNG strains are totally resistant to penicillins irrespective of the dose used.

Valuable information can be gained from programmes that monitor patterns of gonococcal sensitivity to antibiotics, both to examine trends in gonococcal resistance and to assist in formulating treatment regimens appropriate to these changing patterns. The Australia gonococcal surveillance programme

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(AGSP) has noted a decrease in the sensitivity of gonococcal isolates to penicillin and an increase in the incidence of PPNG strains in Australia. We report here the results of continuous surveillance of gonococcal sensitivity to penicillin in Australia during the five years to June 1986. A trend towards increased intrinsic resistance continued during the study period, and a rising incidence of infections with PPNG strains was noted. We observed regional differences in the levels of intrinsic resistance, the incidence of PPNG strain infections, and the proportion of infections with PPNG strains acquired from local, as opposed to overseas, sexual contact. We discuss the implications of these findings for treating gonorrhoea in Australia.

Materials and methods

The data reported in this study were derived from information gathered by the AGSP. The true incidence of gonorrhoea in Australia is unknown, but this continuing multicentric study examines a consistent sample of gonococcal disease predominantly from public sector sexually transmitted disease (STD) clinics. The membership, methods, and quality control procedures of the AGSP have been described previously.² Briefly, participating laboratories are major public health and hospital laboratories located in each state and territory of Australia. Gonococcal isolates obtained in or sent to these centres were examined for their ability to produce β lactamase and tested for sensitivity to selected antibiotics by a standardised agar plate dilution technique. The performance of individual laboratories was assessed by an external quality assurance procedure whereby 50 cultures of N gonorrhoeae (including PPNG strains) were distributed to each participating laboratory each year.

Accepted for publication 21 October 1987

Table 1 Number of isolates of Neisseria gonorrhoeae examined each year, 1981-6

Period	No of isolates	No (%) of PPNG strains				
1981-2	5387	196 (3.6)				
1982-3	6428	249 (3.9)				
1983-4	4999	324 (6.5)				
1984-5	4787	321 (6.7)				
1985-6	4064	515 (12.7)				

PPNG = Penicillinase producing N gonorrhoeae.

In this study, laboratories in each mainland state provided information from 1 July 1981 to 30 June 1986. The sources from which these data were obtained and referral patterns were essentially unchanged throughout the study. Additional material for analysis has been received from Canberra since March 1983, from Hobart since June 1983, and from Darwin since March 1984, but the numbers of isolates from these centres were relatively small. Information about the anatomical site of isolation of each strain, the sex of the infected patient, and the geographical location where infection with a PPNG strain was acquired were recorded for each gonococcal isolate when this information was available. Individual patients were not identified for the purposes of this

study, but each separate presentation was recorded. Multiple isolates from the same patient at each presentation were also recorded, and all infected sites were noted. Strains were classified as being fully sensitive (if the minimum inhibitory concentration (MIC) of penicillin was 0·004–0·016 mg/l), less sensitive (MIC 0·06–0·25 mg/l), relatively resistant (MIC 1·0 mg/l or more) or else as PPNG strains, and were grouped by region and by each quarter from 1 July 1981 to 30 June 1986.

Results

During the five years of the study about 25 000 gonococcal isolates were examined. Table 1 shows the number of cultures obtained in each 12 month period (1 July-30 June). The largest number of strains was examined in 1982-3, and in each following year the total number of isolates examined declined. Most isolates (70%) were from men, and isolates from the urethras of men and the urethras or cervices of women accounted for 85% of strains. Strains cultured from the anorectum or pharynx each comprised fewer than 10% of all gonococci isolated.

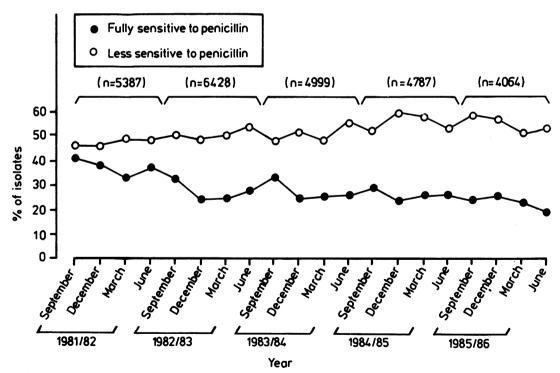


Fig 1 Percentages of all gonococcal strains isolated in Australia in each quarterly period 1 July 1981 to 30 June 1986. (Fully sensitive = minimum inhibitory concentrations (MICs) 0.004-0.016 mg/l, less sensitive = MICs 0.06-0.25 mg/l.)

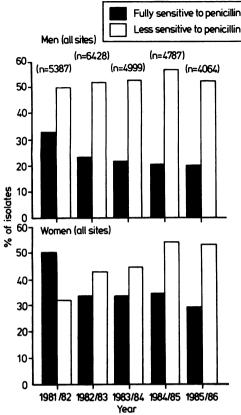


Fig 2 Percentages of all gonococcal strains isolated in Australia from men and women, 1981–6. (See fig 1 for definitions of sensitivities to penicillin.)

INTRINSIC RESISTANCE

Most isolates other than PPNG strains were either fully sensitive or less sensitive to penicillin. Relatively resistant gonococci were uncommon in Australia, accounting for about 2% of all isolates and appearing sporadically. Figure 1 shows the percentage of all isolates that were fully sensitive or less sensitive to penicillin in each quarter of the five year programme. A trend towards increased levels of intrinsic resistance was seen, with the proportion of strains less sensitive to penicillin increasing during the study. This trend towards increased intrinsic resistance was evident in each of the individual centres, but emerged at different times in each location. In Sydney less sensitive strains predominated at the beginning of the study and this trend became more pronounced with time. In Melbourne less sensitive strains predominated from 1982-3 onwards, and in Brisbane this pattern emerged later. Adelaide differed in so far as the trend towards increased resistance was reversed late in 1984, and

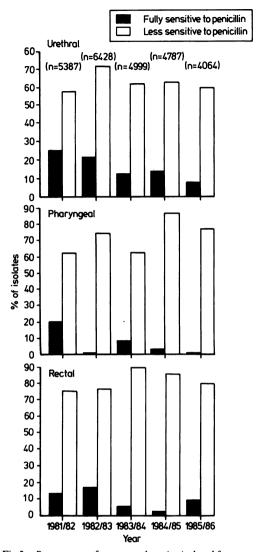


Fig 3 Percentages of gonococcal strains isolated from different anatomical sites of men in Sydney, 1981–6. (See fig 1 for definitions of sensitivities to penicillin.)

fully sensitive strains constituted most isolates until June 1986.

Figure 2 shows higher levels of intrinsic resistance in men than women. It also shows a decrease in the proportion of strains fully sensitive to penicillins in isolates from both sexes during the study period. The levels of sensitivity of organisms isolated from different anatomical sites also differed. Urethral isolates had the highest proportion and pharyngeal isolates the lowest proportion of fully sensitive strains from men, and higher levels of intrinsic resistance were observed in rectal than pharyngeal or urethral isolates.

Table 2 Penicillinase producing strains of Neisseria gonorrhoeae (PPNG) as percentage of all gonococcal isolates in Australia and in five major centres, 1981-6

Period	Australia	Brisbane	Sydney	Melbourne	Adelaide	Perth
1981-2	3.6	5.4	4.9	2.0	1.9	6.4
1982-3	3.9	4.4	3.9	$\overline{2}.\overline{9}$	4.3	6.0
1983-4	6.5	7-1	12.5	3.0	4.0	6.7
1984-5	6.7	4.4	8.7	10.3	2.0	4.8
1985-6	12.7	9.2	20.6	13.8	2.5	9.4

A few PPNG strains were also isolated in Canberra, Darwin, and Hobart.

Figure 3 shows this with data for men from Sydney. In contrast, rectal isolates from women had only slightly higher levels of intrinsic resistance than urethral or cervical isolates from the same group.

PPNG STRAINS

Despite the fall in the total numbers of gonococci cultured during the study period, the incidence of PPNG strains increased as the study progressed both in absolute numbers and as a percentage of all isolates examined (table 1). About 80% of the PPNG strains were obtained from men, this figure varying only slightly in each year of the study. Information regarding the anatomical site of infection was available for most patients. Most (95.5%) of the isolates from men were from the urethra, and the urethra or cervix was the site of most (83.6%) of the isolates from women. Small percentages of the isolates from men were rectal (1.5%) or pharyngeal (2.6%) and these percentages were about three times greater in isolates from women (5.2% rectal and 9.4% pharyngeal). Three cases each of ophthalmic and of disseminated gonococcal infection with PPNG strains were recorded during the study period.

Table 2 shows regional differences in incidence of PPNG strains. A large increase in the incidence of PPNG strains occurred in Sydney in 1983–4 and in Melbourne a year later. The incidence declined in Sydney in 1984–5 but increased again in 1985–6. In contrast, the incidence of PPNG strains in Adelaide for example, remained low throughout the study.

Table 3 shows that in the early years of the study

infections with PPNG strains were mostly acquired overseas, but an increasing proportion of PPNG strains were isolated from patients who had acquired their infection in Australia, this trend being more pronounced in women than men. Regional differences were also noted in the incidence of local versus overseas acquisition of infection with PPNG strains, and table 3 shows examples with data from Sydney and Perth. In Sydney a rapid increase in the number of locally acquired infections with PPNG strains was observed so that by 1983-4 three quarters of the PPNG strains were "local" isolates, almost certainly as a result of spread by infected prostitutes. Despite a partial reversal of that trend the following year, in 1985-6 the high incidence of locally acquired PPNG strains was maintained. This pattern is also currently being observed in Melbourne and Brisbane. In Perth locally acquired infections with PPNG strains rose appreciably in 1983-4, but thereafter the trend was reversed, and most infections with PPNG strains seen at that centre are now contracted overseas. In Adelaide, Hobart, and Canberra PPNG strains were isolated in small numbers, and almost all these infections were acquired in locations outside those centres. Small numbers of PPNG strains were also isolated in Darwin, but some cases were the result of local transmission. Data on the geographical site of acquisition was obtained from about 85% of the 1605 patients infected with PPNG strains recorded in the five year period. Most imported infections were acquired in South East Asia, and 3% of patients infected overseas with a PPNG strain nominated an

Table 3 Source of infection with penicillinase producing Neisseria gonorrhoeae (PPNG) strains in Australia, 1981–6. Percentage of infections contracted locally or overseas in men and women and in two major centres*

Period	n	All PPNG strains acquired:		Strains from men acquired:		Strains from women acquired:		Strains found in Sydney acquired:		Strains found in Perth acquired:	
		Locally	Overseas	Locally	Overseas	Locally	Overseas	Locally	Overseas	Locally	Overseas
1981-2	196	6-1	81-1	5-1	82.0	6.4	74-0	9.6	61-2	8.8	91.2
1982-3 1983-4	249 324	22·0 47·5	67·9	18.8	70·7	42.5	46.8	34-1	56.0	22-2	75.9
1984-5	324	26·1	37·0 52·0	42·4 21·0	41·6 61·9	70·0 50·0	16·6 33·9	74·6 42·0	11·1 39·0	58·3 7·7	41·7 92·3
1985-6	515	44.6	38.6	40.3	45.5	63.8	11.1	65.0	22.9	3.7	96.3

^{*}Data available from about 85% of patients.

area outside Asia or the western Pacific as the geographical location of their sexual contact.

Discussion

The information gathered by the AGSP during the past five years indicates that the sensitivity to penicillin of gonococcal isolates in Australia has changed appreciably. Increased levels of chromosomally mediated intrinsic resistance were observed, and the relative incidence of gonococcal infections caused by PPNG strains also increased.

The raised level of intrinsic resistance seen here was manifested as an increase in the proportion of strains classified as less sensitive to penicillin at the expense of the proportion of fully sensitive isolates. Only a few sporadic cases of infection with relatively resistant gonococci were recorded, so the high level chromosomal resistance reported elsewhere is not yet a problem in Australia.3 We have also been able to document the evolution of increased intrinsic resistance in different regions at different times in this programme by continuous sampling throughout the study. Continuous sampling eliminates distortions in sensitivity patterns as a result of temporal fluctuations in intrinsic resistance.4 The influences that effected these changes in intrinsic resistance have not been examined, but in general the changes were observed earlier and to a greater extent in the larger centres.

The increased levels of intrinsic resistance observed would not of themselves necessitate a change from standard treatment regimens with penicillin and probenecid, an observation in accord with studies in the United Kingdom.⁵ The differences in levels of intrinsic resistance between men and women, however, and in particular the observation that increased levels of intrinsic resistance were seen more often in rectal and pharyngeal isolates from men, has implications for treatment because gonococci are more difficult to eliminate from the rectum and pharynx than from the urethra.6 The desirability of modifying treatment regimens for particular groups of patients has been emphasised in other studies, and recommendations appropriate to Australia have recently been published.8

In this study the numbers of PPNG strains isolated increased while the total number of gonococci cultured was decreasing. PPNG strains were thus responsible for a much greater proportion of gonococcal infections, which further accentuated the impact of these antibiotic resistant strains. In addition, endemic cycles of infection with PPNG strains were noted in some areas, these cycles being superimposed on a pattern of continual importation of these isolates, particularly by patients infected in South East Asia.

As was the case with changes in increased intrinsic resistance, patterns of infection with PPNG strains

were not uniform throughout Australia. In Sydney in 1983, endemic cycles of transmission of β lactamase producing gonococci occurred, which were almost certainly associated with local prostitutes. Similar cycles have continued in Melbourne since 1984 and appear to have been established in Brisbane more recently. In other centres PPNG strains were isolated mostly from infected travellers or their sexual contacts, and there was little evidence of sustained domestic transmission. With high incidences of PPNG strains in the most populous centres in Australia, however, transmission of these strains to other areas seems to be inevitable, and prostitutes and others are known to have travelled between states and infected sexual contacts in areas where PPNG strains are not endemic.

Change from penicillin based treatment regimens has been necessary in centres with high incidences of infection with PPNG strains and endemic cycles of transmission of these strains. For example in Sydney. where the incidence of PPNG strains was more than 20% in 1985-6, ceftriaxone and spectinomycin have been used as alternative treatments.8 Resistance to other antibiotics may arise in Australia. Outbreaks of infections with spectinomycin resistant PPNG strains have been reported elsewhere, although no strains of that type have been detected in Australia. It is important for the control of gonorrhoea that strains of gonococci should continue to be obtained from patients with clinically diagnosed disease and that these isolates are tested for various forms of resistance to antibiotics.

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